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(21) International Application Number: PCT/GB94/01950 (22) International Filing Date: 8 September 1994 (08.09.94) (30) Priority Data: 9318641.9 8 September 1993 (08.09.93) GB (71) Applicant (for all designated States except US): EDKO TRADING AND REPRESENTATION COMPANY LIMITED [TR/TR]; Sisli Bomonti Birahane Sokak No. 40, 80260 Istanbul (TR). (72) Inventors; and (75) Inventors/Applicants (for US only): EMBIL, Koral [TR/TR]; P.O. Box 228, Sisli, 80233 Istanbul (TR). MORTON, Oswald [GB/GB]; 5 St Hilda's Close, Christchurch Avenue, London NW6 7NY (GB). (74) Agents: HOLMES, Michael, John et al.; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MULTI-PHASE COMPOSITIONS FOR AN INITIAL AND DELAYED RELEASE OF A MEDICAMENT		
(57) Abstract There is disclosed a multi-phase composition for treating vaginal infections, for example infections caused by <i>trichomonas vaginitis</i> . The compositions, which are preferably formulated as a cream or pessary, comprise a continuous phase containing anti-vaginitis medicaments for rapid, initial release and porous particles adapted for the delayed release of anti-vaginitis medicaments. Metronidazole is the preferred anti-trichomal medicament.		

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Multi-phase compositions for an initial and delayed release of a medicament

This invention concerns novel pharmaceutical compositions for combating vaginal infections.

It is desirable for a pessary to be able to treat all the common forms of vaginitis, which are most often caused by infection with candida albicans, trichomonas vaginalis or gardnerella sp., either singly or mixed. Commonly derivatives of imidazole and nitroimidazole are used to treat such conditions, examples of such drugs being miconazole, clotrimazole, ornidazole, tinidazole and metronidazole, but despite the good activity of these compounds none has so far individually achieved the broad spectrum of activity required to combat all the common types of infection. Other types of drugs used in such infections include nitrofurfuryl derivatives and various antibiotics.

While such drugs have been formulated as pessaries and vaginal tablets, it has been found for metronidazole that the relapse rate with trichomonal infections (i.e. the rate of reappearance of infection after cessation of the medicament) is higher when administered in this way than when administration is by the oral route. Consequently the oral route is now the preferred route for administration of metronidazole, and pessaries containing this compound have been virtually discontinued. This results in mixed vaginal infections being treated by both the oral and vaginal routes, with consequent inconvenience to the patient.

However, the half life of most anti-vaginitis medicaments is generally relatively short, for example six hours, and it is difficult to formulate a medicament which can effectively be administered only once a day. On the other hand, when starting administration, it is

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preferable to provide a relatively large booster dose of the active substance, so that a delayed release formulation is not entirely satisfactory. Similarly, even when using delayed release, levels of the active substance tend to fall towards the end of the period, for example 24 hours, so that a booster dose may be desirable at intervals during medication.

We have found that it is possible to reconcile the above requirements by providing multiphase formulations comprising a continuous phase containing a relatively large amount of one or more anti-vaginitis medicaments for relatively rapid initial release and containing, dispersed therein, microporous particles containing one or more of the anti-vaginitis medicaments and releasing these over a prolonged period, for example 24 hours.

According to the present invention we provide a pharmaceutical composition for the treatment of vaginitis comprising a continuous phase containing one or more anti-vaginitis medicaments for rapid release and porous particles dispersed therein adapted for delayed release of one or more anti-vaginitis medicaments.

In one embodiment of the invention we provide a cream containing the anti-vaginitis medicament(s) together with porous particles containing one or more of anti-vaginitis medicaments.

The phase in which the medicament(s) are contained may be a conventional cream base, e.g. containing oily or waxy materials such as liquid paraffin, white petroleum or cetyl alcohol, water and one or more surfactants to produce a water-in-oil emulsion. A bactericide such as benzalkonium chloride is conveniently present.

According to a further embodiment of the invention, the compositions take the form of pessaries comprising a pessary base containing the anti-vaginitis medicament(s) and porous particles for delayed release of anti-vaginitis medicament(s).

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The pessary base may be of any conventional material for vaginal administration such as glycerol/gelatin glyco-gelatin, macrogols (polyethylene glycols), natural, synthetic or semisynthetic hard fats, and fractionated palm kernel oil. A particularly preferred material is a hard fat such as cocoa butter (theobroma oil), for instance the range of cocoa butter-based products sold under the trade name Witepsol by Dynamit Nobel, Slough, England.

The pessary base may conveniently contain a surfactant to promote dispersal of the active substances. It may also be advantageous to include a surfactant in the porous particles to aid release of the medicament therein and to promote continuous penetration of the active substances into the mucosal folds.

The surfactant may be a cationic, non-ionic, anionic or amphoteric surfactant although non-ionic surfactants are preferred. Anionic surfactants include salts of long chain alkyl sulphonate esters such as sodium lauryl sulphate, sodium cetostearyl sulphate and sodium tetradecyl sulphate; salts of long chain carboxylic acids such as stearates.

Cationic surfactants include quaternary ammonium or pyridinium compounds such as benzalkonium chloride (a mixture of benzyl alkyl dimethyl chlorides, the alkyl chain ranging from C₈ to C₁₈), tetradecyltrimethyl ammonium bromide and cetylpyridinium chloride.

Amphoteric surfactants include lauryl l-carboxy glycine and lecithins such as soya lecithin.

Non-ionic surfactants include glycol and glycerol esters such as glyceryl monostearate; macrogol esters and ethers such as cetomacrogol; sorbitan and mannitan esters such as sorbitan tristearate; and polyoxyethylene derivatives of such sorbitan esters, for instance polyoxyethylene (20) sorbitan mono-oleate.

The level of surfactant required in the pessary formulation will be readily determined by those skilled

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in the art and will depend on the specific surfactant and the nature of the pessary base; conveniently it is in the range 0.1 to 10 percent by weight, preferably 1 to 5 percent.

It is especially preferred to use a cetomacrogol surfactant in conjunction with a cocoa-butter base such as Witepsol. In such a formulation the surfactant is suitably present in the range 1 to 5 per cent by weight, for instance about 40mg in an overall pessary weight of 2540mg (including active ingredients).

In general, the active substances should include at least one medicament active against trichomonas vaginalis.

Thus one aspect of the invention provides a pessary for human administration comprising an effective amount of one or more drugs active against trichomonas vaginalis, a pessary base and a surfactant.

The preferred antitrichomonal drug is metronidazole.

The use of a surfactant according to the invention allows the active antitrichomonal drug fully to penetrate between the apposed layers of vaginal epithelium which occur in the rugose surface of the vagina so reaching the trichomonas sp. which otherwise would be protected by such apposition from contact with the active ingredients of conventional pessary formulations. The relapse rate when treatment ceases can therefore be expected to be lower than when metronidazole is administered intravaginally in a conventional pessary formulation.

In order to produce a broad spectrum of activity against vaginal infections, it is desirable to include one or more drugs active against candida albicans and/or gardnerella sp. This is particularly desirable since administration of metronidazole alone sometimes results in proliferation of infecting fungal pathogens. A fungicidally active derivative of nitroimidazole such as

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butoconazole or, more preferably, miconazole, is advantageously used as the drug active against candida albicans. Ornidazole, Ketoconazole, Tioconazole and Tinidazole are also suitable fungicidally active agents. Where metronidazole is used as the antitrichomonal drug, it will also be effective against gardnerella sp. However, a broad spectrum antibiotic such as pivampicillin or Clindamycin may advantageously also be included. In order to counter the inflammation and itching associated with vaginitis, it may be beneficial to include a steroidal or non-steroidal antiinflammatory drug such as hydrocortisone or ibuprofen. Lactic acid may also advantageously be included as a further active ingredient.

The pessaries of the present invention may also advantageously include chlorophyll as a deodorant. We have found that although some staining of clothes by the green coloration of the chlorophyll may take place, the surfactant in the composition ensures that such stains are readily removed.

The quantity of metronidazole is conveniently from 500 to 1500 mg per pessary, more preferably from 800 to 1200 mg and suitably about 1000 mg.

The pessary may conveniently contain from 200 to 600 mg of miconazole, more preferably from 240 to 480 mg. The miconazole may be in the form of the free base, especially in the porous particles, or as a salt, for instance the nitrate, especially in the pessary base - a suitable quantity of miconazole per pessary is then about 400 mg.

The porous particles containing anti-vaginitis medicaments may contain two or more such medicaments and/or the composition may contain mixtures of porous particles each containing a different medicament or mixtures of medicaments.

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A wide range of porous particles are available, as described in International Patent Applications WO88/01164 and WO89/10132, United States Patents 4 873 091 and 4690825 and EP-A-306236, the contents of which are incorporated herein by reference.

In such porous particles, the total pore volume is preferably in the range 0.1 to 2.0 ml/g, more preferably 0.3 to 1.0 ml/g. The diameters of the particles will generally be in the range 1 to 1000 microns, preferably 5 to 100 microns, more preferably 10 to 50 microns: the surface area of the particles will generally range from about 1 to 500 m²/g, preferably 20 to 200 m²/g.

The porous particles may be composed of a wide range of materials. Many organic, synthetic polymers are suitable, as well as natural substances such as cellulose or gelatin. The choice of material will depend in part on the intended means of delayed release of the active medicament, i.e. diffusion, compression, dissolving or melting.

Where diffusion of the active medicament is intended, the porous particles may be relatively rigid. This has the advantage that the outermost pores do not collapse when the medicament diffuses out and thus do not block the diffusion of the medicament from the inner pores. Such rigidity can be controlled by the degree of cross-linking of polymeric materials of which the particles are composed. The degree of cross-linking will generally be at least 10%, more usually in the range 20 to 80%, for example 25 to 60%.

Polymers of which the particles may be formed include polyolefins, including polyethylene, polystyrene, polydicyclopentadiene etc.; polyacrylate esters, e.g. optionally alkoxylated C₁₋₁₀ alkyl, cycloalkyl, aryl or aralkyl esters of polyacrylic or polymethacrylic acids; polyvinyl esters e.g. polyvinyl acetate or polyvinyl laurate; polyvinyl ketones, e.g. polyvinylmethyl ketone; and polyvinyl ethers, e.g.

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polyvinylpropyl ether.

As indicated above, the porous particles in such a cream may liberate the active medicament by diffusion, pressure, dissolving or melting. It is preferred that the particles are elastically compressable so that after first application of the cream whereby the medicament contacts the infected area, application of gentle pressure, for example by rubbing, causes rapid release of the active medicament to provide a coating of medicament over the layer of cream.

Elastically compressable particles may be composed of elastomers, such as those described in USP 4 873 091, including for example, isoprene rubbers, butadiene rubbers, chloroprene rubbers, styrene butadiene. Particularly useful are ethylene-propylene-diene terpolymers, wherein the diene components may be straight chain diolefins, cyclic dienes and bicyclic dienes. Examples of such dienes include 1,4-hexadiene, dicyclopentadiene and ethylidene norbornene. Silicone rubbers may also be used.

Porous particles which dissolve, primarily in aqueous body fluids, may be composed of water-soluble gels including gelatin, agarose etc and certain polymethyl methacrylates such as Eudragit (Röhm, Darmstadt) which dissolve at the pH of the vagina.

Porous particles which melt may be composed of fats and waxes of the type used in suppositories which melt at body temperatures but which are solid at room temperature as well as gelatin.

Porous materials for use in compositions of the invention may be made in any convenient way. Thus, it is possible to polymerise one or more suitable monomers in the presence of a dispersed porogen: after polymerisation, the porogen may be removed, e.g. by evaporation or solvent extraction, to provide a network of interconnected pores. The active medicament can then be absorbed into the porous material, if desired by

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first evacuating air from the pores. The active medicament can, however, itself be used as the porogen: the medicament may be dispersed in droplets through a monomer with which it is immiscible so that after polymerisation the active medicament effectively fills pores within the polymeric material. In general, however, it is preferred to prepare the porous material first in order to remove rigorously all traces of monomer, catalysts and cross-linking agents, before introduction of active medicament.

A number of possible methods of manufacture of porous material, in particular porous particles, are described in the prior patents listed above.

In general, porous particles may conveniently be produced by emulsion or suspension polymerisation in a liquid - liquid system. Thus, for example, a solution comprising the chosen water-immiscible monomer, any cross-linking agent required, a catalyst, if needed, and a porogen which is miscible with the solution but immiscible with water. The solution is then suspended in an aqueous solution, which may contain one or more suspending agents or surfactants and polymerisation is initiated e.g. by raising the temperature or by irradiation. The porogen is then removed from the solidified particles, e.g. by evaporation or extraction into a solvent which is substantially inert to the polymer.

Examples of such porogens include C_{5-12} alkanes, C_{5-8} cycloalkanes and aromatic solvents such as benzene toluene etc. The particles will normally be washed thoroughly to remove contaminants, using solvents such that the final solvent can be removed by evaporation.

In general, particle diameter may be controlled by the degree of agitation to prepare the initial emulsion. The pore diameter and pore volume are controlled by the amount of porogen used and the degree of cross-linking.

The monomers used to prepare the particles may be

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any of those appropriate to make the polymers set out above. Suitable cross-linking agents for mono-olefins include poly-ethylenically unsaturated monomers.

The dosage of active medicament(s) contained in the porous particles will vary with the individual medicaments and their half-lives. In general, the ratio of delayed release medicament to rapid release medicament is preferably in the range 1:1 to 5:1, for example 2:1 to 4:1.

The porous particles may be evenly distributed throughout the composition or, in the case of pessaries, may be concentrated in one or more zones, for example in a core.

In general, the size of the porous particles is preferably such that they cannot be taken up into the lymph ducts. On the other hand, large particles give a gritty effect which may produce discomfort. In general, the preferred size range for the porous particles is 10-100 microns.

The following Examples are given by way of illustration only:

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Example 1PessaryComposition of pessary base

Metronidazole	250.0mg
Miconazole nitrate	50.0mg
Witepsol w35	1745.4mg
Cetomacrogol	34.6mg
	<hr/>
	2080.0mg
	per pessary

Composition of microsponges

Metronidazole	500.0mg
Miconazole	100.0mg
both held within polystyrene	
-divinylbenzene porous beads,	
pore volume 0.5 ml/g	

Method of manufacture

The two active ingredients and the surfactant of the base are mixed into the molten Witepsol w35 and the resulting mixture is blended with the pre-prepared porous beads before being poured into pre-cooled moulds. The moulds are passed through a cooling tunnel at -10°C, the pessaries are removed from the moulds and packaged. 0.1% by weight of chlorophyll may be added to both base and microsphere phases.

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Example 2PessaryComposition of pessary base

Polyethylene glycol 4000	900.0mg
Polyethylene glycol 1000	450.0mg
Polyethylene glycol 400	118.5mg
MONATERIC 951A	42.0mg
metronidazole	250.0mg
Tioconazole hydrochloride	100.0mg
pivampicillin	100.0mg
	<hr/>
	1960.5mg
	per pessary

MONATERIC is a surfactant available from Mono Industries Ltd., Paterson, New Jersey, USA.

Composition of porous beads

Metronidazole	500.0mg
Tioconazole	200.0mg
Hydrocortisone	50.0mg
Pivampicillin	50.0mg
blended together and held within	
a polystyrenedivinylbenzene	
porous beads, pore volume 0.5 ml/g	

The pessary is prepared according to the method of Example 1. The MONATERIC 951A may be replaced by MONAQUAT PT-C, PT-L, PT-S or Phospholipid EFA.

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Example 3Pessary

Polystyrene-divinylbenzene porous beads (mean particle diameter 30 microns, pore volume 0.5 ml/g) containing 2g miconazole and 10g metronidazole	25 g
50% Benzalkonium chloride	0.2 g
Hydrocortisone acetate	0.5 g
Metronidazole	12.5 g
Miconazole	2.5 g
Witepsol S55 suppository base	63.65g
Witepsol E85 suppository base	10.65g

The above components apart from the porous particles containing their active ingredients are blended at 55°C, cooled to 40°C and poured into 50 moulds with central pins to make the pessaries formed hollow. After cooling, the pins are withdrawn, the moulds are inverted and porous particles introduced into the cavity left by each pin. The remainder of the cavity is filled with a blend of the two Witepsol bases at 40°C. After chilling, the pessaries are removed from the moulds and packaged.

Example 4Cream

	%
Polystyrene-divinylbenzene porous beads (mean particle diameter 30 microns, pore volume 0.5 ml/g) containing 2g miconazole and 10g metronidazole	25.0
Liquid paraffin	17.75
White petrolatum	8.0
Cetyl alcohol	7.0
Span 60	3.0
Miconazole	0.5
Metronidazole	2.0
Potassium dihydrogen phosphate	0.5
1% Aqueous Benzalkonium chloride	10.0
Tween 60	5.0
70% Aqueous sorbitol	5.0
Hydrocortisone acetate	0.5
Water	15.75

The oily phase comprising the liquid paraffin, white petrolatum, cetyl alcohol and Span 60 are mixed at 60°C. The aqueous phase comprising the remaining components except the porous beads is also blended at 60°C and the two phases combined and homogeneously blended. The porous beads are added subsequently and dispersed throughout the cream.

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Example 5PessaryComposition of pessary base

Metronidazole	250.0mg
Miconazole nitrate	50.0mg
Witepsol w35	1745.4mg
Cetomacrogol	34.6mg
	<hr/>
	2080.0mg
	per pessary

Composition of microsponges

Metronidazole	500.0mg
Miconazole	100.0mg
Sorbitan mono-oleate	190.0mg
each held within polystyrene	
-divinylbenzene porous beads,	
pore volume 0.5 ml/g	

The pessary is prepared according to the method of Example 1.

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Claims

1. A pharmaceutical composition for the treatment of vaginitis comprising a continuous phase containing one or more anti-vaginitis medicaments for initial release and dispersed therein porous particles adapted for the delayed release of one or more anti-vaginitis medicaments.
2. A composition as claimed in claim 1 comprising at least one anti-trichomonal medicament as an anti-vaginitis medicament.
3. A composition as claimed in claim 2 wherein said anti-trichomonal medicament is metronidazole.
4. A composition as claimed in any one of claims 1 to 3 comprising a surfactant.
5. A composition as claimed in any one of claims 1 to 4 comprising one or more drugs active against candida albicans and/or gardnerella sp.
6. A composition as claimed in any one of claims 1 to 5 comprising a broad spectrum antibiotic.
7. A composition as claimed in any one of claims 1 to 6 comprising an anti-inflammatory drug.
8. A composition as claimed in any one of claims 1 to 7 in the form of a cream.
9. A composition as claimed in any one of claims 1 to 7 in the form of a pessary.
10. A process of preparing a composition according to any one of claims 1 to 9, said process comprising

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admixing said anti-vaginitis medicaments and porous particles adapted for the delayed release of anti-vaginitis medicaments together with at least one pharmaceutically acceptable carrier or excipient.

11. Use of a composition as claimed in any one of claims 1 to 9 for the treatment of vaginitis.

12. Use of metronidazole in the manufacture of a composition according to claims 1 to 9 for the treatment of vaginitis.

13. A method of treatment of vaginitis, said method comprising administering intravaginally a composition as claimed in any one of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/02 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 388 718 (ADVANCED POLYMER SYSTEMS INC) 26 September 1990 see page 6 - page 7; example 1 ----	1
A	WO,A,92 10998 (BOMBART F.) 9 July 1992 see page 9; example 7 ----	1
A	EP,A,0 486 117 (EDKO TRADING AND REPRESENTATION COMPANY LTD) 20 May 1992 see page 5; example 1 ----	1
A	WO,A,90 07325 (EDKO TRADING AND REPRESENTATION COMPANY LTD) 12 July 1990 see page 5; example 1 -----	1

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Boulois, D

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